21. (New) A system according to claim 1 wherein said biocompatible chemical gradient stabilizing gel medium is agarose.

22. (New) A system according to claim 1 wherein said chemical attractant is a member selected from the group consisting of folic acid, guinea pig serum, activated complement, bacterial peptides and mammalian chemokines

23. (New) A system according to claim 21 wherein said chemical attractant is folic acid.

REMARKS

Claims 1-7 are under consideration in this application. Claims 1 and 4 have been amended and claims 2, 3 and 5-7 remain as originally presented. New claims 21-23 have been added. No new matter has been introduced.

The applicants' invention is directed to a system for monitoring the effect of extra-cellular chemical stimuli on the translational motion of cells, the system comprising: (a) an array of one or more cell containment wells; (b) an array of one or more chemical attractant wells interspersed among the array of one or more cell containment wells; (c) one or more substantially planar sensing electrodes distributed within the arrays of cell containment wells and chemical attractant wells so that at least one of the sensing electrodes is between one cell containment well and one chemical attractant well, wherein the one or more sensing electrodes is operatively coupled to a sensing device capable of measuring an electrical parameter of the sensing electrode; (d) at least one counter electrode in electrical connection with the one or more sensing electrodes; and (e) a biocompatible chemical gradient gel stabilizing medium in simultaneous diffusional contact with the arrays of cell containment wells and chemical attractant wells.

As originally drafted the claims used the term "volume(s)" which has been replaced by well(s) for containing cells and/or chemical attractant. The term "attractant" has been substituted for agent as originally used. It is noted that volume(s) and well(s) are used interchangeably in the specification. (See for example, page 14, line 17 and page 23, lines 12, 19, 27 and 32.) The same is true for the term "chemical attractant" as now used in the claim for replacing chemical agent. (See for example, page 12, lines 13 and 16, page 14, lines 20 and 24, page 18, lines 12 and 18, page 23, lines 7, 13 and 32 and page 26, lines 6, 15 and 31.)

The Examiner has rejected claim 1-7 under 35 U.S.C. 112 as being indefinite for the broad term "chemical agent volume". As noted above, this term has been replaced by chemical attractant well for

which there is more then adequate support. It is further noted that the specification contains multiple examples of chemical attractants, including folic acid, guinea pig serum, activated complement, bacterial peptides and mammalian chemokines (page 9, 3rd full paragraph and page 18, 1st full paragraph.

The term "chemical agent volume" (replaced by chemical attractant well) can be defined as the chemoattractant- containing well that is the originating point for diffusion of chemical agents that will influence (either positively or negatively) the movement of cells in a directional manner. Likewise, the "cell containment well" is the originating point for migrating cells that will respond to the chemoattractant. The volume of the chemoattractant-containing well and the cell-containing wells is small in relation to the volume of the culture system. In the demonstrated use, these volumes are 2 to 3% of the total volume of the "biocompatible chemical gradient gel stabilizing medium". In the example provided, "chemical attractant well" and the "cell containment well" are wells cut in an agarose gel as one form of "biocompatible chemical gradient gel stabilizing medium". For example, the wells that are formed to hold chemoattractant and cells at the initiation of the assay are usually 1.5 mm in diameter and 5 mm in depth, and contain a volume of approximately 5 to 10 microliters. In the invention, the cells are induced to move across the sensing electrode that has been placed in the path of the moving cells.

The Examiner has also rejected the claims in that the term "biocompatable chemical gradient stabilizing medium" is too broad. This term has been amended to read biocompatible chemical gradient gel stabilizing medium. This gel is preferably agarose. The gel serves as a matrix that allows for the gradient formation by the diffusing chemical attractant. The art is familiar with other such media which include in addition to agarose, polyacrylamide, collagen or other gels. The Examiner is correct that in the case of the agarose gel, the term "biocompatible chemical gradient stabilizing medium" means that cells migrate in and under an agarose environment.

The Examiner has rejected claims 1-7 as obvious (35 U.S.C. 103(a)) over Griaever et al. in view of Nelson et al. It is the Examiner's position that Giaever et al. teach a device for monitoring the activities of living cells in tissue culture using electronic means that Giaever's device comprises a cell culture, wherein chemical agents are contained within the cell culture and wherein electronics are connected to arrays of electrodes contained within the cell culture, the electronic connected to the electrodes within the cell culture also containing chemical agents to monitor the activities of the living cells in tissue culture. The Examiner expressly

acknowledges that Giaever et al. "do not expressly teach all the different types of chemical agents contained within the cell culture, a biocompatible chemical gradient stabilizing medium that is in simultaneous diffusional contact with the arrays of cell containment volumes and chemical agent volumes and all the systems selected parts." It is the Examiner's position however that Nelson et al. supplies the omitted elements.

Giaever et al. are directed to monitoring the activities of cells grown in tissue culture. In Giaever et al., electrodes are deposited by vacuum evaporation in two layers at the bottom of a tissue culture enclosure. AC current of about one microamp and fixed or varying frequencies is applied between a large counter electrode and a small active electrode, while the voltage is monitored with a phase sensitive detector. As a two probe measurement is involved, the active electrode is made small, such that its impedance dominates the measurement. Cells are cultured directly on the small electrodes. As they attach and spread (flatten out) on the electrode surface they cause large changes in electrical impedance of the system. These changes are highly dependent on the type of protein initially absorbed on the electrode surface. The following attachment and spreading cell motion causes cell contacts with the electrode to change with time, and this in turn causes fluctuations in the electrode's impedance.

Giaever et al. do not teach or suggest a manner of measurement that could detect the arrival of cells at a detecting electrode, nor do they indicate the use of stabilizing matrix to sustain gradient formation. There is nothing in Giaever et al. to suggest that a non-liquid matrix such as an agarose gel (the "biocompatible chemical gradient stabilizing medium") would be compatible with the sensitive electronic measurements that are made in accordance with the instant invention, that such measurements would be possible. In fact, as acknowledged by the Examiner, there is no indication that a matrix would be compatible with the electronic measurements contemplated.

In addition, Giaever et al. describe cells that have been deposited directly on the electrode, and do not describe the measurement of movement by cells from a distance to the measuring electrode.

Nelson et al represents the state of the art prior to the instant invention and has been acknowledged as such by the applicants at page 4 of the application. The applicants describe the Nelson assay and conclude with its disadvantages noting that the migration patterns of the cells are observed optically and that they have to be done at many points to get an estimate of the

extent of movement in each assay and that in addition the nature of the measurements obtained render it very difficult to quantify the rate at which the cells move in response to chemotactic stimuli.

There is no indication in Nelson et al. that any other measurement technique could be used other than visual detection. With the visual detection scheme described by Nelson et al., it would not be possible to carry out multiple simultaneous detection of independent chemotactic responses, and the larger the scale, the more complex this problem would become. Moreover, the visual detection method does not allow for the undisturbed monitoring of cell behavior. For example, exposure of cells to illuminating light for microscopy can disturb normal patterns of cell function. The Nelson et al. method is an endpoint assay system: the assay concludes at a fixed point of time, and measurements are taken that prevent the ongoing assessment of the cells (e.g. the cells are fixed and stained at the conclusion of the assay). In accordance with the invention, the measurements are carried out continuously in near-real time, and can be carried out for several days, allowing for the measurement of slow chemotactic responses.

It is submitted that the skilled artisan would not, contrary to the Examiner's assertion, "be motivated to modify Giaever et al's device to include Nelson's teachings for an improved benefit of producing the instantly claimed device of monitoring the activities of cells.

What the Examiner has done is to read back into the prior art the teachings of the invention which came later.

The U.S. Supreme Court has cautioned against "slipping into the use of hindsight" and urged courts "to resist the temptation to read into the prior art the teachings of the invention in issue." *Graham v. John Deere Co.*, 383 U.S. 1, 36, 148 USPQ 459, 474 (1966). For example, impermissible "hindsight" is using knowledge of the solution to determine that the answer to the technical problem was "obvious", whereas to one without knowledge of the solution, the answer was not "obvious" at all.

The impermissible use of hindsight is to combine pieces of the prior art to argue that a combination invention is obvious. There must be something in the prior art that suggested the combination of these particular prior art devices and processes other than the hindsight gained from knowing that the inventor chose to combine these particular things in this particular way. *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 10151, 5 USPQ2d 11434, 1438 (Fed. Cir. 1988).

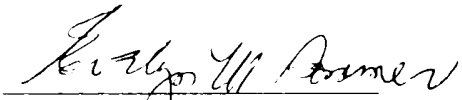
The applicants' device, once disclosed seems obvious and simple. The test is whether the subject matter of the claimed inventions would have been obvious to one skilled in the art at the time the inventions were made, not what would be obvious after reading the patents in suit. *Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082, 1090-002, 227 USPQ 337, 342-43 (Fed. Cir. 1985).

The Examiner has stated that one of ordinary skill would have been motivated to modify Giaever et al. in view of the Nelson teachings. However, various bits of data or teachings of the prior art are not properly combined unless there is something in the prior art itself that suggests that those teachings could or should be combined. Both the suggestion for combining teachings to make the invention and its reasonable likelihood of success "must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chem.*, 837 F.2d 469, 473,5 USPQ2d 1529, 11531 (Fed. Cir. 1988). "Motivated to modify" without more does not meet the test that the invention was obvious.

In this regard, it is pointed out that Nelson et al. was available prior art since 1975 and that in spite of the activity, i.e., tissue culture is an indispensable research tool. In addition, it has played an essential role in the development of modern biotechnology. Some of the powerful new applications are: pharmaceuticals, monoclonal antibodies, vaccines, genetic screening, skin grafts, gene therapy and in vitro toxicology, yet the applicants are the first to propose the instantly claimed method and assay.

In view of the above, reconsideration and allowance of the claims in the application are respectfully requested.

Respectfully submitted,

By: 

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